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Use Of The State Immunization System To Assess Influenza Vaccine Effectiveness Among Children 6-35 Months Of Age In New Haven County, Ct, 2003-2012

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ABSTRACT

Background:

Population-based immunization information systems (i.e., registries) have been used successfully to assess vaccine effectiveness (VE) in children. The Connecticut Immunization Registry and Tracking system (CIRTS) contains electronic entries of individual vaccinations and dates and demographic data for children <5 years with a high participation rate. The Connecticut Emerging Infections Program (CTEIP) has conducted active surveillance for laboratory-confirmed, influenza-associated hospitalizations among children <17 years who reside in New Haven County since 2003. CIRTS and CTEIP provided the opportunity to evaluate influenza VE among young children in New Haven.

Objective:

Our primary objective was to examine the overall effectiveness of full vaccination against influenza in preventing hospitalization of children <3 years old in New Haven County from January 1, 2003 – March 31, 2012, using CIRTS as our source of information. Our secondary objective was to access the overall VE of having ever received at least one dose of influenza vaccine in protecting against hospitalization.

Methods:

A matched case-control study was conducted to examine VE. Cases were children 6-35 months old hospitalized with confirmed influenza in New Haven County 2003-2012 who were "active" in CIRTS ($\geq$ 1 vaccination recorded in CIRTS after the birth hospital admission). Five controls per case were matched based on birthdate and zipcode of residence. Data on vaccination status for both cases and controls was obtained from CIRTS. Up-to-date for childhood vaccines was based on having age-appropriately received 3 doses of DTaP (children <15 months) or MMR (children $\geq$15 months). Full vaccination against influenza was based on CDC's annual recommendation on influenza vaccination. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in both matched and unmatched analyses using logistic regression and controlling for age-group (1 year intervals), up-to-date status and race/ethnicity. VE was calculated as (1 – OR) x 100%.

Results:

A total of 104 case children and 520 controls were studied. The odds of being a case were significantly ($p<0.05$) higher for non-Hispanics, blacks and unknown race/ethnicity than for non-Hispanic whites (OR= 1.96, 1.88 and 3.21;$P<0.05$ respectively). Overall, 11.5% of cases were fully vaccinated against influenza and 29.8% had ever received any influenza vaccination compared to 14.2% and 37.3% of controls, respectively. The adjusted VE in matched analysis of full vaccination compared to no vaccination was 31% (95% CI, <0%-69%; p=0.38). The adjusted VE of at least one dose of influenza vaccine compared to no vaccination was 37% (95% CI, <0%-63%; p=0.09).

Conclusion:

Our study suggests that the overall total VE is unlikely to be greater than 69% among children 6-35 months of age and having had at least one dose of influenza vaccine could be protective from influenza-caused hospitalization compared with never having been vaccinated. This study should be extended for several more influenza seasons to determine a range of effectiveness that does not include zero.

Study background and objectives:

Influenza vaccine effectiveness is (VE) an important measure in understanding how well a vaccine works in the real world setting[1].Since VE can range widely among different populations and from season to season, it is important to assess and confirm the value of flu vaccination as a public health intervention. Rapid assessment of VE is essential in influenza pandemics to establish optimal vaccination strategy [2]. Studies comparing the VE of one and two does of flu vaccine would also provide evidence for vaccination recommendations. Because of recent changes in vaccination recommendations, many more young children are now receiving vaccinations to protect against influenza. However, influenza VE has not been well characterized in young children and very few studies have focused on VE over the long term.

Understanding the VE of influenza vaccine is essential in making vaccination recommendations for the public and can help optimize the vaccine distribution strategy in an outbreak setting. Population-based immunization information systems (i.e., registries) have been used in several studies as an alternative data source for vaccination information on those in the studies to assess vaccine effectiveness (VE) in children[3][4][5]. In these studies, no patient contact was necessary, only demographic information and information on vaccinations recorded in the registry were used to determine VE. The results were comparable to the more traditional and labor intense approach of non-registry-based case-control studies [2][3]. Although more information for additional analyses could be gained via the traditional approach involving contact with individuals (e.g., day care attendance, medical risk factors for hospitalization with influenza), using the immunization information system is more cost-effective since it requires fewer personnel and much less time, and it is possible to retrospectively evaluate vaccine effectiveness over a longer period of time.

The Connecticut Immunization Registry and Tracking system (CIRTS), was implemented statewide in 1998 and contains electronic entries of individual vaccinations and dates and demographic data for children <5 years. It automatically enrolls children born in Connecticut. Although it is possible for a parent/guardian to opt out, the participation rate is relatively high at approximately 90%. In addition, vaccination information completeness is high due to active efforts to ensure all routine childhood immunizations are reported. CIRTS has been used to evaluate effectiveness of pneumococcal conjugate and rotavirus vaccines in young children [2][3]. The Connecticut Emerging Infections Program (CTEIP) is a collaboration between the State of Connecticut Department of Public Health, the Yale School of Public Health, and the Centers for Disease Control and Prevention. Since 2003, it has conducted active surveillance for laboratory-confirmed, influenza-associated hospitalizations among children from birth to age17 years who reside in New Haven County. Information on cases is collected from medical records and includes: demographic information, street address of residence, hospitalization dates, underlying conditions, and vaccination history in addition to influenza testing, treatment, and complications. The use of data from immunization registry and case-based surveillance system enables us to examine influenza VE in a relatively easy and rapid way. It also can provide insight into the overall, multiyear impact of the vaccine recommendations in practice at a lower cost than could be done with a series of more conventional case-control studies done using vaccination data from interview and medical records and identification of controls from clinical sources or random digit dialing.

Influenza vaccination was first recommended for children <2 years beginning in 2003-2004. The recommendation was expanded to include all children < 5 years in 2006.There have been few published studies of influenza VE in these age groups. One, a registry-based study in New York City found that a single dose of vaccine against H1N1 during the 2009 pandemic was ineffective in preventing hospitalization in <3 year olds but highly effective in older children [3]. A case-control study conducted in a single pediatric practice also found that partial vaccination was

ineffective among children aged 6 to 23 months but highly effective for children aged 24 to 59 months in preventing medically attended, laboratory-confirmed influenza[6]. Another prospective observational cohort study in Finland found that a single dose of trivalent inactivated influenza vaccine was effective in preventing influenza in young children aged 9 months to 3 years[7]. In 2010 and 2011, WHO convened annual meetings to assess the effectiveness of pandemic (H1N1) 2009 influenza vaccines in clinical trials by reviewing studies in Europe, China, the USA and Canada. The studies showed that a single dose of pandemic inactivated vaccine was sufficient for older children while a second dose of vaccine was needed to boost immune responses in infants and toddlers 6 months to 3 years of age[8][9]. These studies are limited to a single influenza season and do not shed light on the overall, multiyear impact of the vaccine recommendations in practice. Importantly, the recommendations for influenza vaccination from CDC varied over years and the definition of full vaccination has changed. For example, for season 2003-2006 , it is recommended that a child <9 years should be vaccinated with 2 doses of vaccine in the first influenza season in which he/she gets vaccinated. Subsequently, a single dose each year is deemed sufficient. However, if only one dose is received in the first year, only a single dose is needed in each subsequent year. None of the studies fully addressed the permutations of the number and timing of influenza vaccination.

Our primary objective is to examine the overall effectiveness of full vaccination against influenza in preventing hospitalization of children under 3 years old in New Haven County, Connecticut from January 1, 2003- March 31, 2012, using CIRTS as our source of information. Our secondary objective is to access the overall effectiveness of having ever received at least one dose of influenza vaccine in protecting against hospitalization.

Subjects, Materials and Methods:

A matched case-control study was conducted to examine VE. Cases were children aged 6 months to 35 months old when hospitalized with confirmed influenza infection any time from December 1, 2003 through March 31, 2012. For each case, 5 controls were selected from the Connecticut birth registry and matched with cases on date of birth (up to $\pm$ 15 days if needed) and zip code of residency. This was done to minimize the potential for differential exposure and vaccination opportunities that may be associated with socioeconomic status and/or geography. To assure that all cases and controls had the potential to have their influenza vaccinations captured in CIRTS, children included in our study were assigned to have had at least 1 routine vaccination other than a birth dose of hepatitis B recorded in the system.

Information on vaccination status of each case and control was extracted from CIRTS, which includes each vaccine given since birth , dates administered and the type of vaccine used(e.g., for influenza, inactivated or live-attenuated). Sex and race were also extracted from CIRTS. Vaccination history against diphtheria-tetanus-pertussis (Dtp) and measles-mumps-rubella (MMR) was used to define a child's up-to–date immunization status. The up-to-date status was defined as having at least 3 doses of DTP/DTaP vaccine for children under 15 months and having at least 1 MMR vaccine dose record in CIRTS for children above or equal to 15 months. These criteria were used for simplicity and because of high acceptance in Connecticut of DTP/DTaP(recommended to have 3 doses by age 6 months) and of MMR (recommended at 12-15 months of age) based on vaccine coverage data. All data on cases and controls were entered into an Excel database. Children not registered or opted out of CIRTS and those without 1 vaccination record other than hepatitis B vaccine at birth were excluded. To ensure a 1:5 case to control ratio, excluded controls were replaced by qualified controls with the closest birth dates and same zip codes as cases.

A child was considered vaccinated if a dose of vaccine was received≥14 days prior to hospitalization for cases, and of the matched cases during the same influenza season for controls. Influenza seasons generally were defined as

beginning in September in one year and ending in May the ensuing year.

Fully vaccinated was defined according to CDC's annual guidelines for influenza vaccination (Table1).It was recommended that children under 9 years old receiving vaccine for the first time to receive 2 doses of vaccine for satisfactory antibody responses. Generally, a child was considered fully vaccinated if a) 2 doses of vaccine were received in the current season or b) 2 doses of vaccine were received for the first time in the previous season and 1 dose of vaccine was received in the current season. For the influenza seasons 2003-2006, only 1 dose of vaccine was needed if a child had not received two doses of the vaccine the first time they were vaccinated. For seasons 2007-2009, children recommended for vaccination who were in their third or more year of being vaccinated and who received only 1 dose in each of their first 2 years of being vaccinated only needed a single annual dose to be considered fully vaccinated. For the season 2010-11, due to the H1N1 outbreak in 2009,most children were required to have 2 doses of vaccination during 2010-11 except for children who received at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine, and 2 doses seasonal vaccines for the first time during 2009-2010 or children who received at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine and at least 1 dose seasonal vaccines (not for the first time) during 2009-2010. For season 2011-2012, because the vaccine strains were unchanged from the 2010-11 season, only 1 dose of the 2011-12 vaccine was required if a child received at least 1 dose of the 2010-11 seasonal vaccine. Partially vaccinated was defined as having had at least one dose of influenza vaccine at any time but not qualifying for fully vaccinated. Our study divided all cases and controls into 3 categories in terms of their vaccination status: fully vaccinated, partially vaccinated, and never vaccinated.

The data were analyzed using SAS version 9.2 (Cary, NC) for Microsoft in Windows. The total VE was determined by first calculating the matched OR among fully vaccinated children and never vaccinated children using conditional logistic regression with 1:5 matching, then calculating effectiveness using the formula (1-OR)x 100%. Similarly, the VE of having ever received at least one dose of vaccination was calculated for all children. Race (non-Hispanic white and all others), age group (children aged 6-11 months, 12-23 months and 24-35 months), and up-to-date status were adjusted for in our regression model. Based on preliminary data from CIRTS, for children in the birth cohorts from 2003-2008, 54% had received at least one dose of influenza vaccine, 38% at least 2 doses and 14% at least 3 doses. In order to have an 80% power to get 50% VE with 95% confidence with an expected control vaccination rate of 50%, one would need 89 cases and 445 controls.

Since CIRTS may not capture all doses of flu vaccine received by a child and it was not known whether cases were more or less likely than controls to be underreported, a sensitivity analysis was done comparing influenza vaccination status in EIP case records with case influenza vaccination records in CIRTS. The case records in EIP were considered to be complete since they were ascertained via telephone interview and confirmed with hospitals. Using the level of influenza vaccine under-reporting found on comparing EIP with CIRTS case records, analyses of VE for full vaccination versus no vaccination and VE for having at least one dose of vaccine versus no vaccination were calculated with the following 3 assumptions: cases were equally as likely to be underreported as controls; cases were 10% more likely to be underreported than controls; and cases were 10% less likely to be underreported than controls.

This study was reviewed and approved by the human subjects review boards at Yale and at the Connecticut Department of Public Health.

Results:

From 2003 through the 2011-12 influenza seasons, 146 children 6-35 months of age were hospitalized with laboratory-confirmed influenza after excluding those that occurred between April and November 2009 during the H1N1 pandemic before vaccine was widely available. A total of 42 cases were excluded for not having records in CIRTS or not meeting the vaccination requirement. Finally, 104 eligible cases were included in our study. 5 controls were matched by date of birth and zip code to each case, resulting in 520 control children.

Table1 shows the CDC recommendations for influenza vaccination from 2003-2012.

Figure1 shows the number of cases by year and their vaccination status from 2003-2012. In general, the number of cases decreased over time with more than half (59.6%) occurring early in the study period, 2003-2006.

Table2 shows selected characteristics of cases and controls and the odds of being a case compared with the control group. About half of the cases were in the 12-23 month old age group. Sex and up-to-date status were not significantly different for cases and controls. However, the odds of being a case were significantly ($p<0.05$) higher for non-Hispanics, blacks and unknown race/ethnicity than for non-Hispanic whites (OR= 1.96, 1.88 and 3.21, respectively).

Table3 shows vaccine effectiveness for the unmatched analysis. The VE of full vaccination is 28%(95% CI, <0%-63%), the VE of partial vaccination is 29%(95% CI, <0%-59%), and the VE of having ever received at least one dose of influenza vaccine is 29%(95% CI, <0%-55%).

Table4 shows the analysis of vaccine effectiveness by age group, by up-to-date status. The VE of having ever received at least one dose of influenza vaccine in children aged 24-35 months is 67% (95% CI, <0%-89%,p=0.05) but not significant in other age groups or by up-to-date status. The VE of full vaccination and partial vaccination are not significant in all age groups or by up-to-date status.

Table5 shows the estimates for the total VE and the VE of having ever received at least one dose of influenza vaccine in protecting against hospitalization. The matched OR for total VE is 0.69 (95% CI, 0.31-1.57, p=0.38), point estimate of total VE is 31% (95% CI, <0%-69%; p=0.38). The matched OR for having at least one dose of influenza vaccine is 0.63 (95%CI, 0.37-1.08, p=0.09), point estimate of the VE of having ever received at least one dose of influenza vaccine is 37% (95% CI, <0%-63%; p=0.09).

Table6 shows the results of the comparison of case influenza vaccination status based on the EIP case report versus CIRTS. Overall, CIRTS records were only 63.6% complete compared to EIP records, an under-reporting rate of nearly 40% (36.4%). The rate of underreporting decreased over time from 48% for 2003-2006 to 18% for 2007-2012.

Table7 shows the VE estimates using different assumptions about under-reporting, all centered around 40% under-reporting of influenza vaccination status. For VE of full vaccination versus no vaccination, point estimates of VE ranged from a statistically significant 48% when the assumed underreporting rate was 40% for cases and 50% for controls to a statistically insignificant 11% when the assumed underreporting rate was 50% for cases and 40% for controls. Assuming under-reporting was equal for both, the point estimate of VE was 31% with an upper limit of 61%. For VE of at least one dose of vaccination versus no vaccination, point estimates of VE ranged from a statistically significant 66% when the assumed underreporting rate was 40% for cases and 50% for controls to a statistically insignificant 10% when the assumed underreporting rate was 50% for cases and 40% for controls. Assuming under-reporting was equal for both, the point estimate of VE was 50% (95%CI, 5%-61%, p=0.03).

Table 8 and **Figure 2** show the percentage of vaccinated controls from 2003-2012. Vaccination levels increased over time from 27.9% with any vaccination and 20% with partial vaccination in season 2003-2005 to 60% with any vaccination and 41.7% partial vaccination in season 2009-2011.

Table 1. CDC recommendation for influenza vaccination 2003-2012

Season	Recommendation
2003-06[10][11][12][13][14]	• 2 doses administered >1 month apart are recommended for satisfactory antibody responses for children receiving vaccine for the first time. • If a child aged <9 years receiving vaccine for the first time does not receive a second dose of vaccine within the same season, only 1 dose of vaccine should be administered the following season.
2007-2009[15][16][17][18]	• 2 doses administered >1 month apart are recommended for satisfactory antibody responses for children receiving vaccine for the first time. • 2 vaccine doses for children aged 6 months-8 years who received an influenza vaccine for the first time in the previous season but who did not receive the recommended second dose of vaccine within the same season • Children recommended for vaccination who are in their third or more year of being vaccinated and who received only 1 dose in each of their first 2 years of being vaccinated should continue receiving a single annual dose.
2010-11[19]	• 2 doses administered >1 month apart are recommended for satisfactory antibody responses for children receiving vaccine for the first time. • Children aged 6 months-8 years who received a seasonal vaccine for the first time during 2009--2010 but who received only 1 dose should receive 2 doses. • In addition, children aged 6 months-8 years who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine should receive 2 doses of a 2010-11 seasonal influenza vaccine, regardless of previous influenza vaccination history. • Children aged 6 months-8 years who received at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine, and received 2 doses seasonal vaccines for the first time during 2009-2010, only 1 dose of vaccine should be administered. • Children aged 6 months-8 years who received at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine, and received 1 dose seasonal vaccines (not for the first time) during 2009-2010 , only 1 dose of vaccine should be administered.
2011-12[20]	• 2 doses administered >1 month apart are recommended for satisfactory antibody responses for children receiving vaccine for the first time. • Children aged 6 months through 8 years who received at least 1 dose of the 2010-11 seasonal vaccine will require only 1 dose of the 2011-12 vaccine because the 2011-12 vaccine strains are unchanged from the 2010-11 season. • Children aged 6 months through 8 years who did not receive at least 1 dose of the 2010-11 seasonal influenza vaccine, or for whom it is not certain whether the 2010-11 seasonal vaccine was received, should receive 2 doses of the 2011--12 seasonal influenza vaccine

Figure 1: Number of cases 2003-2012

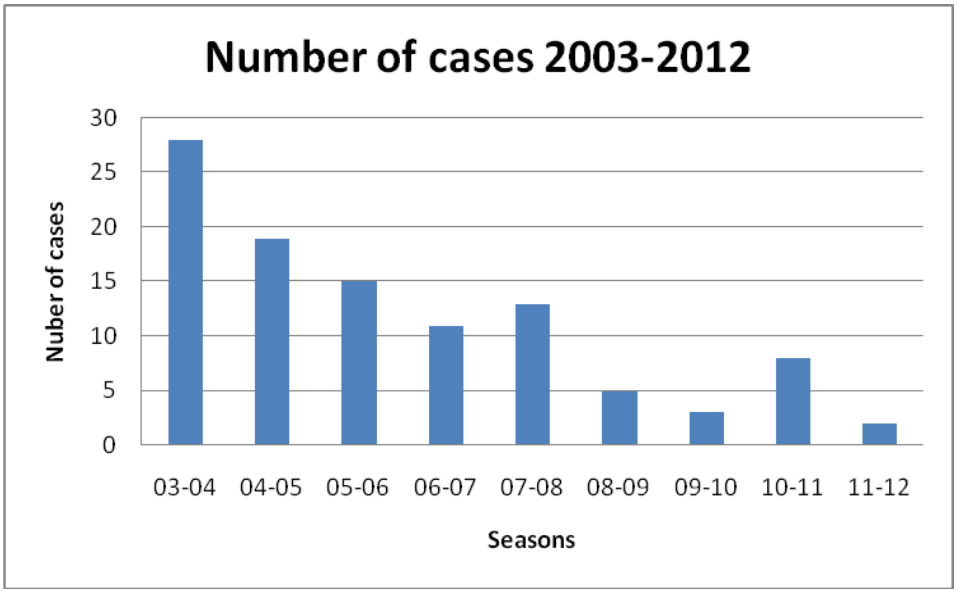


Table 2. Comparison of cases and controls by selected features[a]

	Cases (n=104)	Controls (n=520)	OR(95%CI)	P Value
Age (years)	1.44 ± 0.63	1.44 ± 0.63		1.00
Age group(months)				1.00
6-11	29(27.9)	145(27.9)		
12-23	51(49.0)	255(49.0)		
24-35	24(23.1)	120(23.1)		
Sex				NS
Male	52(50.0)	284(54.6)	Ref	
Female	52(50.0)	236(45.4)	1.20(0.79,1.83)	
Race				0.01
White	28(26.9)	217(41.7)	Ref	
Hispanic	40(38.5)	165(31.7)	1.88(1.11,3.17)	0.02
Black	22(21.2)	87(16.7)	1.96(1.06,3.61)	0.03
Asian	2(1.9)	22(4.2)	0.71(0.16,3.16)	NS
Unknown	12(11.5)	29(5.6)	3.21(1.47,6.99)	<0.01
Up-to-date[c]				NS
Yes	94(90.4)	479(92.1)	Ref	
No	10(9.6)	41(7.9)	1.24(0.60,2.57)	NS

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.

[b] P-value is for t-test (continuous variables) or for χ^2 test (categorical variables).

[c]Children ≤15 months with ≥3 doses of Dtp and Children>15 months with ≥ 1 dose of MMR were defined as up-to-date.

Table 3. Vaccine effectiveness, unmatched crude analysis

Vaccination group	Cases	Controls			
	N(%)	N(%)	OR (95%CI)	P value	VE (95% CI)
Fully	12(11.5)	74(14.2)	0.72(0.37,1.40)	NS	28%(<0%-63%)
Partially	19(18.3)	120(23.1)	0.71(0.41,1.22)	NS	29%(<0%-59%)
Any	31(29.8)	194(37.3)	0.71(0.45,1.13)	NS	29%(<0%-55%)
Never	73(70.2)	326(62.7)	Ref	-	-

Table 4. Analysis of vaccine effectiveness by age group, by up-to-date status.

Vaccination group	Cases	Controls			
	N(%)	N(%)	OR (95%CI)	P value	VE (95% CI)
Age 6-11 months					
Fully	2(17.2)	27(18.6)	0.28(0.06,1.28)	NS	72%(<0%-94%)
Partially	6(10.3)	38(26.2)	0.60(0.22,1.61)	NS	40%(<0%-78%)
Any	8(27.6)	65(44.8)	0.47(0.20,1.13)	NS	53%(<0%-80%)
Never	21(72.4)	80(55.2)	Ref	-	-
Age 12-23 months					
Fully	9(15.7)	39(12.9)	1.23(0.56,2.79)	NS	<0%(<0%-44%)
Partially	10(21.6)	45(20.0)	1.19(0.54,2.60)	NS	<0%(<0%-46%)
Any	19(37.3)	84(32.9)	1.21(0.65,2.26)	NS	<0%(<0%-35%)
Never	32(62.8)	171(67.1)	Ref	-	-
Age 24-35 months					
Fully	1(4.2)	8(6.7)	0.47(0.06,3.97)	NS	53%(<0%-94%)
Partially	3(12.5)	37(30.8)	0.30(0.09,1.09)	NS	70%(<0%-91%)
Any	4(26.7)	45(37.5)	0.33(0.11,1.04)	0.05	67%(<0%-89%)
Never	20(83.3)	75(62.5)	Ref	-	-
Up-to-date					
Fully	12(12.8)	73(15.2)	0.74(0.36,1.50)	NS	53%(<0%-94%)
Partially	18(19.2)	118(24.6)	0.69(0.37,1.25)	NS	70%(<0%-91%)
Any	30(31.9)	191(39.9)	0.71(0.43,1.16)	NS	67%(<0%-89%)
Never	64(68.1)	288(60.1)	Ref	-	-
Not up-to-date					
Fully	0 (0)	1 (2.4)	-	-	-
Partially	1(10)	2 (4.9)	2.11(0.17,25.9)	NS	<0%(<0%-83%)
Any	1(10)	3 (7.3)	1.41(0.13,15.2)	NS	<0%(<0%-87%)
Never	9(90)	38 (92.7)	Ref	-	-

Table 5. Vaccine Effectiveness, matched analysis

	Cases	Controls			VE (95%CI)
	N(%)	N(%)	OR[a] (95%CI)	P Value	
Fully VS never vaccinated	12(14.1)	74(18.5)	0.69(0.31,1.57)	NS	31% (<0%-69%)
Any VS never vaccinated	31(29.8)	194(37.3)	0.63(0.37,1.08)	0.09	37%(<0%-63%)

[a]Matched Odds Ratio

[b]Number of children with full vaccination or have at least one dose of vaccine.

Table 6. Percentage of influenza cases found vaccinated in CIRTS compared to in EIP case records by time period, 2003-2012.

Data source	2003-2006	2007-2012	Total
	No. with an influenza vaccine record	No. with an influenza vaccine record	No. with an influenza vaccine record
EIP	33	22	55
CIRTS	17	18	35
Percentage of EIP in CIRTS	51.5%	81.8%	63.6%
Underreporting rate	48.5%	17.2%	36.4%

Table 7. Vaccine Effectiveness, using varying assumptions on underreporting rates.

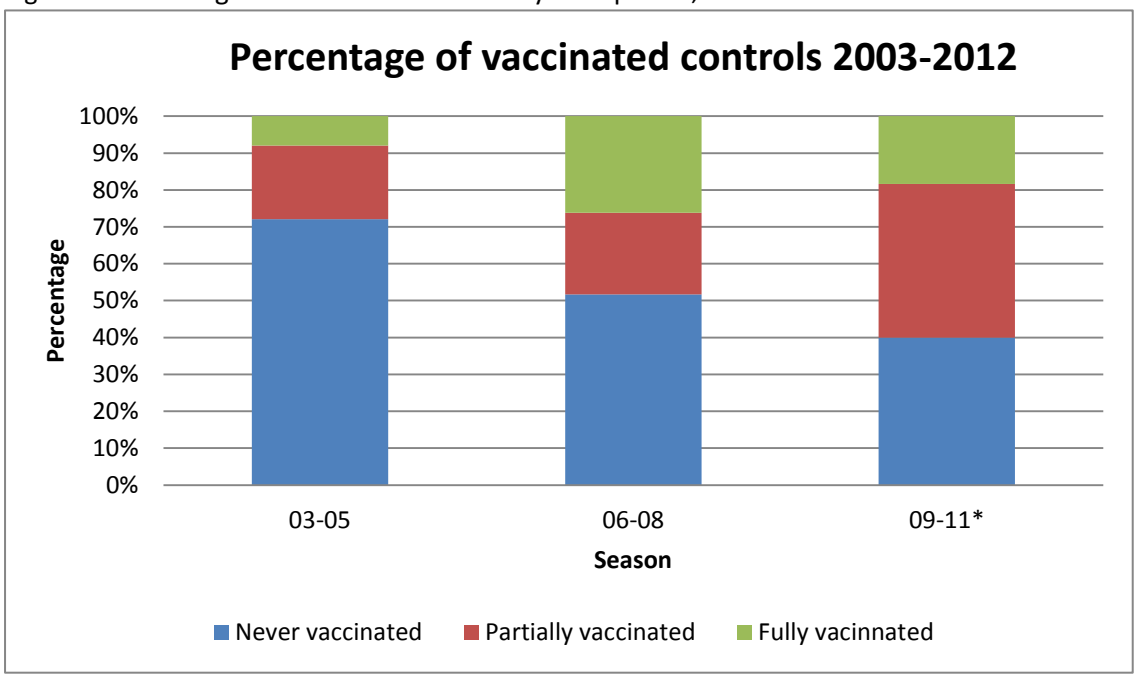
Underreporting rates for cases and controls	Cases N (%)	Controls N(%)	OR (95%CI)	P Value	VE (95%CI)
Fully VS never vaccinated					
40% cases and controls	20(23.5)	123(30.8)	0.69(0.39,1.23)	NS	31%(<0%-61%)
50% cases , 40% controls	24(28.2)	123(30.8)	0.89(0.51,1.53)	NS	11%(<0%-49%)
40% cases , 50% controls	20(23.5)	148(37.0)	0.52(0.29.0.93)	0.02	48%(7%-71%)
Any VS never vaccinated					
40% cases and controls	52(50.0)	323(62.1)	0.61(0.39,0.95)	0.03	50%(5%-61%)
50% cases , 40% controls	62(59.6)	323(62.1)	0.90(0.59,1.38)	NS	10%(0%-41%)
40% cases , 50% controls	52(50.0)	388(74.6)	0.34(0.22,0.52)	<0.001	66%(48%-78%)

[a]Matched Odds Ratio

Table 8. Percentage of vaccinated controls, 2003-2012

Season(%)	03-05	06-08	09-11
Fully vaccinated	7.9	26.2	18.3
Partially vaccinated	20.0	22.1	41.7
Any vaccination	27.9	48.3	60.0
Never vaccinated	71.1	51.7	40.0

Figure 2: Percentage of vaccinated controls by time period, 2003-2012.



*season 09-10 to season 11-12

Discussion:

Our study has several important findings despite their lack of statistical significance. First, it shows the VE of full vaccination versus no vaccination is 31% with an upper 95% confidence limit of 69% and that the VE of ever having had at least one dose of influenza vaccine versus no vaccination is 37% with an upper 95% CI of 63%. These estimates suggest that the overall total VE is unlikely to be greater than 69%. Second, we found that there was significant under-reporting of influenza vaccination to the immunization registry, resulting in lower than expected influenza vaccination rates and loss of power to fully establish a range of effectiveness that did not exclude zero.

Our VE estimates are somewhat lower than but overlapping with the estimates found in the few other studies that have evaluated influenza VE among young children [21] .A study by CM Shuler et al. on VE against medically attended laboratory-confirmed influenza among children aged 6 to 59 months in 2003-2004 showed VE of full vaccination versus no vaccination of 49% (95% CI, 30%-60%). Partial vaccination had no significant protective effect among children aged 6 to 23 months, but had a significant VE of 65 %(95% CI, 30%-60%) among children aged 24 to 59 months [6]. A large-scale study on seasonal Influenza VE among children aged 6 to 59 months in southern China also found that full vaccination was highly protective against infection with a VE of 51.8% (95% CI, 41.3%–60.4%) and partial vaccination was only protective for children aged 24 to 59 months with a VE of 32.4% (95% CI,19.2%–43.5%)[22]. Another prospective case-control study among children with medically attended, acute respiratory infections showed that the VE of full vaccination versus no vaccination was 44% (95% CI, <0%-78%) in 2003-2004 and 57% (95% CI, 28%-74%) in 2004-2005[23]. However, all of these studies looked at VE in preventing influenza infection and none of them assessed influenza VE in preventing hospitalization. Of interest, since several papers grouped children 24-35 months with older children and found more benefit, we looked at this age group by itself and found that the VE of at least one dose of influenza vaccine versus no vaccination was higher in children in this age range at 67% with a 95% CI of 0%-89%. Our founding is consistent with Schuler's study that partial vaccination had a significant VE among children aged 24 to 59 months. This suggests that this age group be considered separately from younger children when examining VE in young children. The founding of significant VE of partial vaccination among children aged 24 to 59 months in Shuler's study is consistent with our founding.

The finding that influenza vaccination was under-reported to CIRTS by nearly 40% raises questions about using CIRTS to continue VE studies. To assess the magnitude of impact from under-reporting on our study results, we conducted a sensitivity analysis comparing influenza vaccination statues in EIP case records with case influenza vaccination records in CIRTS. The case records in EIP were considered to be complete since they were ascertained via telephone interview and confirmed with hospitals. Several assumptions were used to examine the difference in VE. Our sensitivity analysis suggests that the effect of under-reporting is mainly to reduce power without strongly affecting the point estimate of VE if under-reporting is equal for cases and controls. However, our study would underestimate the VE if under-reporting is higher in controls than cases. On the other hand, the VE would be overestimated if under-reporting is higher controls than cases. This analysis is important to determine the performance of CIRTS and whether it is a valid method for future VE assessment. Since there is an increasing trend of influenza vaccination among young children and the under-reporting rate of CIRTS has decreased substantially during recent years, our study suggests that CIRTS could be continued to use to expand this influenza VE study in future and could provide more accurate estimates.

There are some additional important limitations of our study. First, since VE varies from season to season, the estimated overall VE cannot reflect the variation among seasons, including that VE could be very high during some

seasons. However, our objective is to assess the overall performance of influenza vaccination overtime. Therefore, it is reasonable to examine the point estimate of VE over time. Second, CDC's recommendations for influenza vaccination are not consistent over years. Before 2007, getting one dose of vaccine in the previous season and one dose in the current season is treated as fully vaccinated. This is different from our current perception of full vaccination. However, we have no cases and only 5 controls with this situation, thus our results are unlikely to be affected. Finally, as mentioned before, with a low vaccination rate, the sample size of our study is too small to detect a statistically significant VE and subgroup analysis is restricted. In this context, this study can be considered a pilot study using population-based immunization information systems (i.e., registries) as an alternative data source to assess influenza vaccine effectiveness (VE) overtime in children.

Our study has implications for future research using immunization registries to study influenza VE. First, this study can be expanded to increase sample size by including cases from more seasons or combining data from other states with established immunization registries. Where registries have data on older children, VE in other age groups could be studied. Given the potential issues with under-reporting of influenza vaccination, it is important to determine whether there are biases in reporting of vaccinations for cases compared to controls. Researchers may need to contact controls as well as cases to confirm their vaccinations and estimate the underreporting rate for controls.

Conclusion:

Our study suggests that the overall total influenza VE over the past 9 years in protecting children 6-35 months of age is unlikely to be greater than 69% and that partial vaccination can also be protective. This study should be extended for several more influenza seasons to determine a range of effectiveness that does not include zero, and efforts should be made to determine whether there is any bias in under-reporting of influenza vaccination in cases compared to controls. Population-based, well-established childhood immunization registries have the potential to enable a simple, rapid assessment of long-term VE in children.

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